Traditional Chinese medicine for activating blood circulation and detoxifying in unstable angina pectoris: A systematic review and meta-analysis

Ying Zhang, Hua Qu, Xiaojuan Ma, Dazhuo Shi

Objective: The purpose of this review was to evaluate the effectiveness of traditional Chinese medicine for activating blood circulation and detoxifying (ABCD) in patients with unstable angina pectoris.

Methods: We performed an electronic literature search of six medical databases for relevant articles published up to December 2014. Randomized controlled trials that compared ABCD Chinese medicine (alone or alongside conventional drugs) with conventional drugs or other Chinese medicines alone were included. A meta-analysis was performed for the following outcome measures: reduction of angina symptoms, electrocardiogram improvement, blood lipid levels, inflammatory factor levels, and plasma fibrinogen levels.

Results: In total, 11 moderate- to low-quality studies involving 686 patients were included. The evidence indicated that ABCD Chinese medicine exhibited superior effectiveness in relieving angina symptoms compared with conventional drugs [relative risk, 1.23; 95%

Abbreviations: ABCD, activating blood circulation and detoxifying; UAP, unstable angina pectoris; RCTs, randomized controlled trials; RAS, reduction of angina symptoms; ECG, electrocardiogram; FIB, fibrinogen; CI, confidence interval; RR, relative risk; ACS, acute coronary syndrome; MI, myocardial infarction; hs-CRP, high-sensitivity C-reactive protein; CBM, Chinese Biological Medicine; CNKI, China National Knowledge Infrastructure; VIP, Chinese Scientific Journal database; WFDP, WanFang Digital Periodicals; WMDs, weighted mean differences; FAA, frequency of angina attacks; DAA, total duration of angina attacks in 24 h; SRRN, stopping or reducing rate of nitroglycerin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol (LDL-C); TNFα, tumor necrosis factor alpha; CRP, C-reactive protein.

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Introduction

Although therapeutic strategies for coronary heart diseases have greatly advanced and mortality rates have decreased in Western countries over the past few decades, mortality and morbidity associated with these diseases are still increasing in China, where a large number of patients are diagnosed with acute coronary syndrome (ACS). ACS includes unstable angina pectoris (UAP), non-ST-elevated myocardial infarction (MI), and ST-elevated MI, which describe different degrees of myocardial ischemic states. UAP is the most common clinical presentation of ACS. Conventional medications for UAP include aspirin, angiotensin-converting enzyme inhibitors, beta-blockers, calcium antagonists, and nitrates. However, all these drugs may have undesirable effects. For example, aspirin can potentially increase the incidence of hemorrhage and some patients have acquired resistance to the drug.

Traditional Chinese medicine has become a popular treatment for UAP. According to modern medical theory, platelet activation, thrombosis, and inflammation are central to UAP pathogenesis. In contrast, according to traditional Chinese medicine, blood stasis is at the core of UAP development. If blood stasis is not eliminated, it results in the production of toxins over time. Therefore, numerous modern medical studies have been conducted on the use of traditional Chinese medicine for activating blood circulation and detoxifying (ABCD). Basic studies have revealed that ABCD can decrease tissue damage and the expression of inflammation-related factors in the rat model of carotid artery thrombosis, inhibit the nuclear factor kappa B pathway and decrease matrix metalloproteinase-9 in the aorta of apolipoprotein E knockout mice, decrease serum high-sensitivity C-reactive protein (hs-CRP) levels, decrease apoptosis and oxidative damage to umbilical vein endothelial cells induced by oxidized low-density lipoprotein, and inhibit coagulation and platelet activation in a rat model of acute MI.

In clinical practice, ABCD Chinese medicine has been found to exhibit add-on effects in UAP patients; it can enhance the effectiveness of conventional medicine in relieving angina symptoms, decrease the dosage of nitroglycerin, and minimize adverse effects. However, evidence supporting or disproving these cardiovascular protective effects has not been systematically reviewed. We therefore conducted this study to systematically and objectively evaluate the clinical efficacy of ABCD Chinese medicine for UAP based on a comprehensive understanding of previous studies and meta-analyses of randomized controlled trials (RCTs).

Methods

Search strategy

We performed an electronic literature search using the following databases: PubMed (1989–December 2014), Web of Science (1990–December 2014), Chinese Biological Medicine (CBM; 1990–December 2014), China National Knowledge Infrastructure (CNKI; 1989–December 2014), Chinese Scientific Journal (VIP; 1989–December 2014), and WanFang Digital Periodicals (WFDP; 1989–December 2014). There were no language restrictions. We used the following English search terms alone or in combination: “traditional Chinese medicine,” “activating blood circulation and detoxifying,” “unstable angina pectoris,” “randomized controlled trials,” “controlled trials,” and “randomly.” Chinese search terms included generic names for UAP (“Bu_wen_ding_xing_xin_jiao_tong”), ABCD (Huo_xue_jie_du or Hua_yu_jie_du), frequently used herbal formulae for ABCD (Wu_wai_xia_du_yin, si_miao_yong_an_tang or Xian_fang_huo_ming_yin), and randomized (Sui_ji).

Study selection

The inclusion criteria for studies were as follows: RCTs; inclusion of patients diagnosed with UAP according to accepted criteria; comparison of ABCD Chinese medicine as an intervention or co-intervention (alongside conventional drugs for UAP) with no treatment, placebo, other types of Chinese medicines, or conventional drugs; measurement of the effectiveness of ABCD Chinese medicine for UAP by a reduction in angina symptoms (RAS), electrocardiogram (ECG) improvement, and laboratory indices.

Data extraction and methodological quality assessment

Two investigators (Ying Zhang and Xiaojuan Ma) evaluated all studies and independently extracted relevant data from each using a structured table. To resolve any disputes, a third investigator (Dazhuo Shi) was consulted. The following data were extracted: number of patients in experimental and control groups, age, UAP diagnostic criteria, intervention, treatment duration, and outcome...
measures. Two authors independently assessed the risk of bias in the included studies using criteria recommended in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. This risk was judged as high for studies that met all criteria, unclear for studies with insufficient information for judgment, and low for studies that met none of the criteria.15

Statistical analysis

Dichotomous data were analyzed using relative risks (RRs) and continuous variables were analyzed using weighted mean differences (WMDs); effect sizes were indicated by 95% confidence intervals (CIs). Statistical heterogeneity was measured using the $I^2$ statistic. Fixed-effect models were applied if there was no significant heterogeneity across studies ($I^2 < 50\%$); otherwise, random-effects models were applied. All $P$-values were two-tailed, and the threshold for statistical significance was set at 0.05. Cochrane Collaboration software (RevMan 5.2, Copenhagen, Denmark) was used to perform statistical analyses. There is no registered protocol for the present meta-analysis.

Results

Based on our inclusion criteria, we identified 1098 potential studies from our initial search and excluded 644 trials for duplicated publications. Subsequently, 108 potential trials were identified, 97 of which were excluded for specific reasons (Fig. 1). Eventually, only 11 RCTs met our inclusion criteria.

Characteristics of the included studies

The characteristics of the 11 included RCTs are listed in Table 1. The RCTs collectively involved 686 patients and were published between 2002 and 2014. All patients were residents of the People’s Republic of China. Of this total, 352 patients received ABCD Chinese medicine alone or in combination (experimental group). The treatment course ranged from 2 to 4 weeks, and RAS and ECG improvement were the most common outcome measures. Serum hs-CRP and blood lipid levels were the most commonly measured laboratory indices.
Quality assessment of the included studies

All 11 RCTs mentioned the term randomization, but only three described it in detail. None mentioned allocation concealment or intention-to-treat analysis. Because not all the trial protocols were accessible, the extent of selective reporting was generally unclear (Figs. 2 and 3).

Effects of interventions

RAS

RAS was evaluated in eight studies including 529 patients, with 274 in the experimental group and 255 in the control group. A random-effects model was used to analyze the data according to heterogeneity testing ($I^2 = 78\%$).

<p>| Table 1 Characteristics of the trials included in this meta-analysis. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size T/C</th>
<th>Mean age T/C</th>
<th>Diagnosis standard</th>
<th>Course (week)</th>
<th>Experimental group</th>
<th>Control group</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng et al., 2014</td>
<td>30/31</td>
<td>61.9/61.4</td>
<td>2007 CDTGUANSTEMI</td>
<td>4</td>
<td>Xiongshao capsule + Huanglian capsule + CD</td>
<td>Xiongshao capsule + CD</td>
<td>hs-CRP BL</td>
</tr>
<tr>
<td>Pei et al., 2012</td>
<td>32/32</td>
<td>61.94/60.36</td>
<td>2007 CDTGUANSTEMI</td>
<td>3</td>
<td>Guizhi fuling decoction + Huanglian jiedu decoction + CD</td>
<td>CD</td>
<td>RAS BL hs-CRP</td>
</tr>
<tr>
<td>Zhang et al., 2004</td>
<td>45/30</td>
<td>58.89/58.77</td>
<td>1979 ISFC/WHO</td>
<td>4</td>
<td>Tongmai jiedu decoction</td>
<td>CD</td>
<td>RAS ECG</td>
</tr>
<tr>
<td>Zhao et al., 2007</td>
<td>42/38</td>
<td>52.52/50.24</td>
<td>2000 CDTGUANSTEMI</td>
<td>2</td>
<td>Huayu jiedu decoction</td>
<td>CD</td>
<td>RAS CRP SRRN</td>
</tr>
<tr>
<td>He et al., 2007</td>
<td>30/30</td>
<td>61.96/62.93</td>
<td>1979 ISFC/WHO</td>
<td>4</td>
<td>Huoxue jiedu decoction + CD</td>
<td>CD</td>
<td>RAS ECG hs-CRP</td>
</tr>
<tr>
<td>Chen et al., 2009</td>
<td>30/31</td>
<td>61.24/61.84</td>
<td>2007 CDTGUANSTEMI</td>
<td>2</td>
<td>Xiongshao capsule + Huanglian capsule + CD</td>
<td>Xiongshao capsule + CD</td>
<td>RAS ECG hs-CRP</td>
</tr>
<tr>
<td>Pan et al., 2010</td>
<td>38/38</td>
<td>58.23/57.69</td>
<td>GCRNDTCM</td>
<td>4</td>
<td>Qingre jiedu huoxue decoction + CD</td>
<td>CD</td>
<td>RAS ECG</td>
</tr>
<tr>
<td>Gao et al., 2014</td>
<td>33/32</td>
<td>65.9/67.2</td>
<td>GCRNDTCM</td>
<td>2</td>
<td>Quyu jiedu decoction + CD</td>
<td>CD</td>
<td>RAS ECG hs-CRP</td>
</tr>
<tr>
<td>Zeng et al., 2009</td>
<td>28/25</td>
<td>58.2/56.4</td>
<td>2000 CDTGUANSTEMI</td>
<td>2</td>
<td>Xuebijing injection + CD</td>
<td>CD</td>
<td>RAS ECG hs-CRP</td>
</tr>
<tr>
<td>Peng et al., 2012</td>
<td>20/20</td>
<td>61/60.6</td>
<td>2007 CDTGUANSTEMI</td>
<td>2</td>
<td>Shuxin tongbi decoction + CD</td>
<td>CD</td>
<td>RAS ECG</td>
</tr>
<tr>
<td>Wang et al., 2002</td>
<td>20/23</td>
<td>63.5/64.8</td>
<td>2000 CDTGUANSTEMI</td>
<td>2</td>
<td>Huangqi injection + Luotai injection + Jiedu huxin capsule + CD</td>
<td>CD</td>
<td>CD62P vWF</td>
</tr>
</tbody>
</table>

CDTGUANSTEMI: Chinese diagnosis and treatment guidelines of unstable angina and non-ST segment elevation myocardial infarction; GCRNDTCM: Guidelines of clinical research of new drugs of traditional Chinese medicine; ISFC/WHO: International Society and Federation of Cardiology/World Health Organization; hs-CRP: high-sensitivity C-reactive protein; BL: blood lipid; FAA: frequency of angina attacks; DAA: duration of angina attack; RAS: reduction of angina symptoms; ECG: electrocardiogram; SRNN: stopping or reducing rate of nitroglycerin; TNFα: tumor necrosis factor alpha; AE: adverse event; FIB: fibrinogen; T/C: treatment/control; CD62P: P-selectin protein; vWF: von Willebrand factor; CD: conventional drugs.

Fig. 2  Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies.
Overall, the outcomes showed a statistically significant difference in favor of the experimental group (RR, 1.23; 95% CI, 1.05–1.44; \( P < .001 \); Fig. 4). This indicated that ABCD Chinese medicine exhibited superior effectiveness in relieving angina symptoms.

**ECG improvement**

Six studies including 377 patients, with 196 in the experimental group and 181 in the control group, analyzed ECG improvement. Data were analyzed using a random-effects model according to heterogeneity testing (\( I^2 = 87\% \), \( P < .00001 \)). Overall, the results showed that ABCD Chinese medicine produced no significant ECG improvement compared with control interventions (RR, 1.21; 95% CI, 0.91–1.62; \( P = .19 \); Fig. 5).

**Serum blood lipid levels**

Four studies involving 247 patients, with 124 in the experimental group and 123 in the control group, reported serum blood lipid levels, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The results indicated that ABCD Chinese medicine significantly lowered TC, TG, and LDL-C levels and increased HDL-C levels compared with control interventions. The details are shown in Table 2 and Fig. 6.

**Anti-inflammatory effects**

Five studies analyzed serum hs-CRP levels. After pooling these trials, we observed that ABCD Chinese medicine significantly decreased hs-CRP levels (WMD, \(-0.86\); 95% CI, \(-1.14 \sim -0.57\); \( P < .00001 \)). Data concerning tumor necrosis factor alpha (TNF\(\alpha\)) and CRP were extracted from two trials; a summary of these indices is shown in Table 3 and Fig. 7. Overall, we noted that ABCD Chinese medicine exhibited better anti-inflammatory effects with regard to serum hs-CRP and TNF\(\alpha\) levels compared with control interventions.

**Anticoagulant effects**

Plasma fibrinogen (FIB) levels were measured in two trials. ABCD Chinese medicine significantly decreased FIB levels (WMD, \(-0.58\); 95% CI, \(-0.95 \sim -0.21\); \( P = .002 \); Fig. 8). Furthermore, one trial claimed that CD62p (P-selectin protein) decreased from 8.69 ± 2.11% to 5.40 ± 1.46% with ABCD Chinese medicine, while vWF decreased from 142.47 ± 17.06% to 110.58 ± 18.57%.
Other outcomes

One trial reported the frequency of angina attacks (FAA) and the total duration of angina attacks in 24 h (DAA) as outcomes. Compared with control interventions, ABCD Chinese medicine significantly decreased FAA (3.50 times/week to 6.22 times/week; \( P < .05 \)) and DAA (10.68 min/d to 27.91 min/d; \( P < .05 \)). Another trial reported the stopping or reducing rate of nitroglycerin (SRRN) as an outcome; this was 90.48% and 68.42% in the experimental and control groups, respectively.

Publication bias

Because of the insufficient number of included trials, we did not use a funnel plot to detect publication bias.

Adverse effects

Only one trial reported adverse events in the form of mild diarrhea in four patients in the experimental group that disappeared after dose reduction. No severe adverse events were reported.

Discussion

This systematic review analyzed evidence for 686 patients included in 11 RCTs. The pooled results showed significant RAS and superior anti-inflammatory, anticoagulant, and lipid-lowering effects for ABCD Chinese medicine. To the best of our knowledge, the present meta-analysis is the first to evaluate the efficacy of ABCD Chinese medicine for UAP.

Systemic markers of inflammation have been found in patients with UAP. Disruption of culprit coronary stenosis may cause a greater inflammatory response in patients with unstable angina than in those with stable angina. Our study showed that ABCD Chinese medicine decreased TNFα and hs-CRP more than did conventional therapy. Therefore, anti-inflammation might be one of the mechanisms by which ABCD Chinese medicine exerted its protective effect on UAP patients.

Recently, several meta-analyses on herbs, TCM formulae, or Chinese patent medicines for angina pectoris have been published. One study suggested that combination therapy with Xuefu Zhuyu decoction and conventional drugs is more beneficial and effective in treating angina pectoris compared with conventional drugs alone, and that Xuefu Zhuyu decoction may be a better choice for the treatment of stable angina pectoris (SAP).

Another of these meta-analyses indicated that Chinese patent medicines could improve the survival of angina patients who consumed Western medicines. Yet another systematic review showed that compound salvia pellet, a Chinese patent medicine, could relieve angina symptoms and improve ECG results with few adverse effects. However, neither these studies nor the present study can draw definitive conclusions from the results because of the following limitations.

First, most of the included studies provided insufficient information about randomization procedures. Unsuccessful randomization can lead to selection bias while allocating interventions to participants. Second, none of the studies were double-blind trials, even though blinding is very important to ensure that patients have equivalent experiences and that each patient has an equal chance of being allocated to one or other of the conditions during the course of the study.
clinical trial procedure. Third, none of the included trials mentioned allocation concealment, withdrawal, or dropout events. Fourth, although UAP is a lifelong disease, all included trials featured short-term outcomes because of the absence of follow-ups. This could also explain why the incidence of adverse events was too low for safety evaluations. Fifth, as described previously, we only searched Chinese and English databases. However, herbal medicines are also used commonly in other Asian countries such as Japan and Korea. This may have led to a potential selection bias, thus limiting external generalization of evidence.

In addition to quality limitations, the estimates of some outcomes were limited by small sample sizes. The sample size in all trials was <100 and could have influenced the precision of estimates. Even so, we believe this meta-analysis is of great importance because it at least provides moderate evidence regarding the effectiveness of ABCD Chinese medicine for UAP in clinical settings. Further

### Table 3

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Included studies</th>
<th>WMD and 95% CI</th>
<th>P-value</th>
<th>Heterogeneity</th>
<th>P-value for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP (mg/L)</td>
<td>10,11,13,14,15</td>
<td>-0.86 [−1.14, −0.57]</td>
<td>&lt;0.00001</td>
<td>2%</td>
<td>0.39</td>
</tr>
<tr>
<td>TNFα (ng/mL)</td>
<td>9,17</td>
<td>-5.05 [−7.51, −2.59]</td>
<td>&lt;0.0001</td>
<td>99%</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>9,10</td>
<td>-3.33 [−12.35, 5.30]</td>
<td>0.43</td>
<td>99%</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

CI: confidence interval; hs-CRP: high-sensitivity C-reactive protein; TNFα: tumor necrosis factor alpha; CRP: C-reactive protein.
studies should explore the mechanisms of action of ABCD Chinese medicine in UAP patients.

Conclusions

The present study provides preliminary evidence that supports the continued use of ABCD Chinese medicine as a potentially optimistic and reliable intervention for UAP. Further work is needed to improve understanding of this treatment using rigorously designed, multicenter, large-scale clinical trials that investigate the effectiveness and safety of ABCD Chinese medicine for UAP.

Author contributions

Study conception and design: Dazhuo Shi.
Performance of experiments: Ying Zhang, Xiaojuan Ma, Dazhuo Shi.
Data analysis: Ying Zhang, Xiaojuan Ma.
Contribution of reagents/materials/analysis tools: Ying Zhang.
Manuscript writing: Ying Zhang.
Manuscript revising: Hua Qu.

Conflicts of interests

The authors declare that they have no competing interests.

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